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## Neuroimaging of Intracranial Atherosclerotic Disease

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### 1. Introduction

Ischemic stroke is now universally accepted as a heterogeneous disease. The need to properly classify stroke subtypes is increasingly driven by the realization that different mechanisms may require different treatments. Also the risk of recurrent vascular events differs among various ischemic stroke subtypes.

Intracranial atherosclerotic disease (ICAD) is fast emerging as the predominant mechanism of ischemic stroke in the world and particularly in patients of Asian origin (Kim et al, 2006 and Sacco et al, 1995). Also, ICAD is reported to have the highest risk of recurrent ischemic cerebrovascular events being quoted between 25-30% in two years (Wong et al, 2003 and Mazighi et al, 2006).

### 2. Epidemiology

It is now well recognized that intracranial atherosclerotic disease predominantly affects patients of Asian, African and Hispanic origin. Since these are the regions of the world which are going to harbor the majority of the world's stroke population, it is expected that the disease burden of intracranial atherosclerosis is also going to increase.

The rates of ICAD reported from Asian countries range between 33-56% depending on what cutoff for stenosis is taken (Huang et al, 1997 and Lee et al, 2003). Caucasians predominantly have extracranial atherosclerosis and rates of intracranial disease vary between 1 and 24% (e.g., Sacco et al., 1995; Wityk et al., 1996).

Data on the prevalence of asymptomatic stenosis are relatively scarce. Warfarin versus Aspirin in Symptomatic Intracranial disease (WASID) trial reported presence of 27% asymptomatic disease in patients who also had symptomatic stenosis (Nahab et al, 2008). Studies of healthy Japanese and Korean populations report asymptomatic disease in 3-3.5% (Park et al, 2006 and Wong et al, 2007). There is a growing need to identify the asymptomatic entity as the process of atherosclerosis can potentially be stalled by timely risk factor management. Several diagnostic modalities are now available and evolving but the focus so far is on the diagnosis of the disease at a stage when it becomes symptomatic.

In this chapter we describe the various radiological presentations of stroke secondary to intracranial atherosclerotic disease followed by a description of the tools available for diagnosing the condition. Non invasive modalities are the main focus as the prevalence of the disease increases and the need to identify asymptomatic disease is also increasingly felt.

Additionally, with a greater number of patients now being offered endovascular treatment, there is a need to have cost-effective, minimally invasive and reliable methods to follow these patients up.

### **3. Infarct patterns**

Literature now exists on infarct patterns associated with intracranial large artery atherosclerosis. The underlying mechanisms leading to ischemia in the diseased arterial territory include artery-to-artery embolism, thrombosis leading to complete occlusion or to local branch occlusion and hemodynamic compromise (Wong et al, 2002). A combination of these factors may also co-exist in some patients. Depending on the mechanism of ischemia, the infarct pattern may differ.

#### **3.1 Border-zone infarctions**

Border-zone infarctions have been described with intracranial atherosclerotic disease for decades. Recently the concept of border-zones has been revisited and two types of border-zone infarctions have been described (Yong et al, 2006). Internal border-zone infarctions involve the area between the territory of anterior, middle and posterior cerebral arteries and the territory supplied by the lenticulostriate, anterior choroidal and Heubner arteries. The term cortical border-zone is used for areas located between the cortical supply of the anterior and middle cerebral arteries (anterior cortical border-zone) and between middle and posterior cerebral arteries (posterior cortical border-zone). It is proposed that the two types of infarctions may have different underlying pathophysiology.

##### **3.1.1 Cortical border-zone infarctions**

For the cortical border-zone infarctions, artery-to-artery embolism has been proposed as causative since the 1980's. Several studies (Torvik et al, 1982, Pollanen et al, 1990, Masuda et al, 1994, Belden et al, 1999) describe border-zone or watershed infarctions resulting from atheromatous large vessel intracranial disease. With Transcranial Doppler monitoring this mechanism has been further validated. Using this modality, impaired clearance of emboli has been documented with middle cerebral artery (MCA) stenosis and patients with this condition were found to have multiple small cerebral infarcts especially in the border-zone territories of MCA with anterior and posterior cerebral arteries (Wong et al, 2002).

##### **3.1.2 Internal border-zone infarctions**

For internal border-zone infarctions, hemodynamic compromise is believed to be the proximate cause. Infarct patterns described include single lacunes in internal border-zone or a string of pearls or scattered pearl appearance on diffusion weighted imaging (DWI) (Turtzo et al, 2009). The underlying mechanism is believed to be a gradual reduction in the perfusion pressure in the stenosed artery. This leads to development of collateral blood supply from branches of extracranial carotid artery. With progression of disease, these collaterals are unable to maintain the hemodynamics and maximal hypoperfusion occurs in the terminal zones of the distribution of MCA and its perforators. These are the internal border-zone areas and the association of these infarcts with increased oxygen extraction fraction has been documented suggesting hemodynamic compromise as the likely mechanism (Yamauchi et al, 2009).

3.2 Cortical territorial infarctions

Cortically based infarctions in the territory of MCA (anterior territorial infarctions) and PCA (posterior territorial infarctions) have also been described with large vessel atherosclerotic disease. The proposed mechanism is again artery to artery embolism. In case of anterior circulation, as opposed to cardioembolic infarcts, these are usually smaller, and limited to one of the three MCA territories. This can be explained based on the size of cardiac emboli which are larger and likely to give rise to large infarcts. However, with larger emboli occluding proximal MCA or distal internal carotid arteries (ICA), large territorial infarctions may also be seen particularly in the absence of effective collaterals (Rovera et al, 2005). The ischemic cortical lesions may co-exist with smaller cortical or subcortical acute lesions resulting from fragmentation of the embolus.

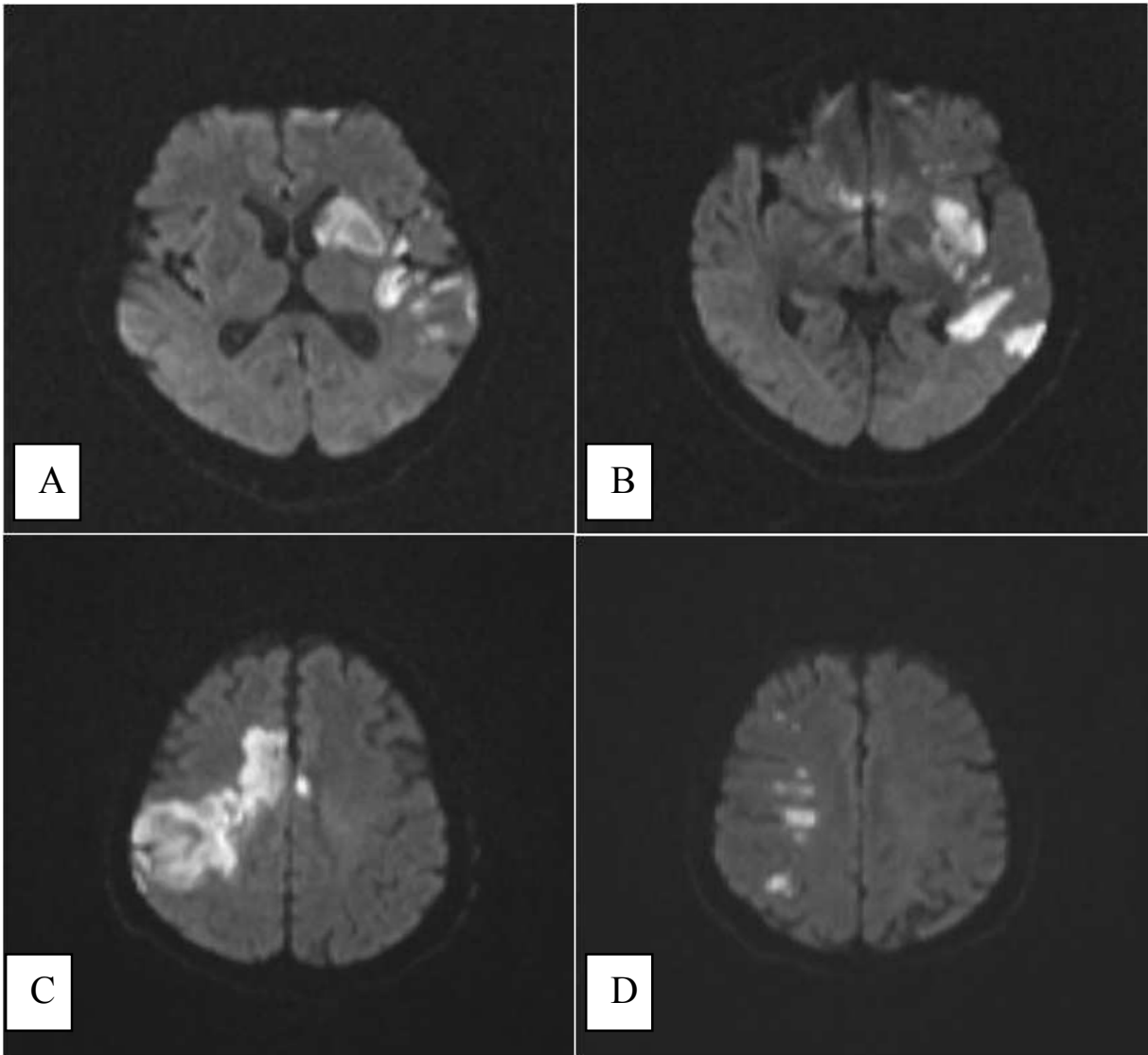


Fig. 1. Diffusion Weighted Images of Infarct Patterns seen with ICAD. A) Multiple infarcts in Right MCA territory, B) Deep MCA perforator infarct along with patchy cortical infarcts, C) cortical infarct in posterior MCA territory, D) String of pearls pattern in Internal border-zone. (Image Courtesy, Stroke Fellowship Program, Aga Khan University Hospital, Karachi, Pakistan)

In the posterior circulation, large artery atherosclerosis involving the vertebrobasilar arteries leads to infarctions in the territories of posterior inferior cerebellar artery (PICA), superior cerebellar artery (SCA) and PCA. Small territorial and nonterritorial cerebellar infarcts are also described with vertebrobasilar disease (Amarenco et al, 1994).

### **3.3 Lacunar infarctions**

Lacunar infarctions in the centrum semiovale have also been described with intracranial atherosclerotic disease. When large (>1.5 cm) and present in the internal border-zone, these are thought to result from hemodynamic compromise. When small (<1.5 cm) they may arise secondary to artery to artery embolism. In this case, they may be accompanied by other small acute infarcts in the same large artery territory (Bogousslavsky and Regli, 1992). Posterior circulation lacunes have also been described with large vessel disease, particularly when they occur in isolation.

### **3.4 Perforator artery infarctions**

With atherosclerotic involvement of MCA, local branch occlusion has also been described leading to deep perforator artery infarctions. Pial infarctions, those occurring in the vascular territories supplied by the superior and inferior branches of MCA have also been described with MCA disease (Lee et al, 2005). Thrombotic occlusion in the former and distal embolization in the latter is thought to be the underlying mechanism.

### **3.5 Multiple acute brain infarctions**

Multiple acute brain infarctions, particularly in the same arterial territory have also been described (Roh et al, 2000 and Kang et al, 2003). The mechanism is believed to be distal embolizations from large vessel unstable plaque. Such infarcts are typically located in a single anterior or posterior arterial territory, but anatomic variations may explain other patterns such as involvement of anterior and posterior circulations simultaneously in case of a fetal-PCA or posterior communicating artery patency, or involvement of bilateral ACA territories in case of a single ACA supplying both hemispheres.

## **4. Imaging of vessels**

The diagnosis of intracranial atherosclerotic disease rests on either direct visualization of the vessels or determination of their flow characteristics. Several non-invasive modalities like magnetic resonance angiography (MRA), computerized tomographic angiography (CTA) and transcranial doppler (TCD) are now available for screening and diagnostic purposes. However, the gold standard for diagnosis is still catheter based conventional angiography.

### **4.1 Catheter based conventional and Digital Subtraction Angiography (DSA)**

DSA has been the reference standard for evaluation of intracranial stenosis and occlusion for decades. The technique involves injection of a radio-opaque dye via an intra-arterial catheter. Usually the femoral or radial arteries are used. Cerebral angiography is performed after catheterizing the cerebral arteries. The term digital subtraction angiography is used when a computer based software subtracts two images that are obtained before and after administration of contrast media. Modern DSA also incorporates three-dimensional reconstructed images which provide even better details.



DSA has several advantages over other modalities used for assessing intracranial stenosis. It provides excellent visualization of the anatomy of the vessel, the severity and length of stenosis and the presence of collateral circulation. However, the major disadvantage lies in the high skill required to perform the study. Another disadvantage is the morbidity associated with the procedure including stroke, arterial dissections, puncture site infection, thrombosis of punctured artery leading to limb ischemia and formation of pseudoaneurysms. In addition to this it carries the risk of nephrotoxicity associated with iodinated contrast used in the procedure.

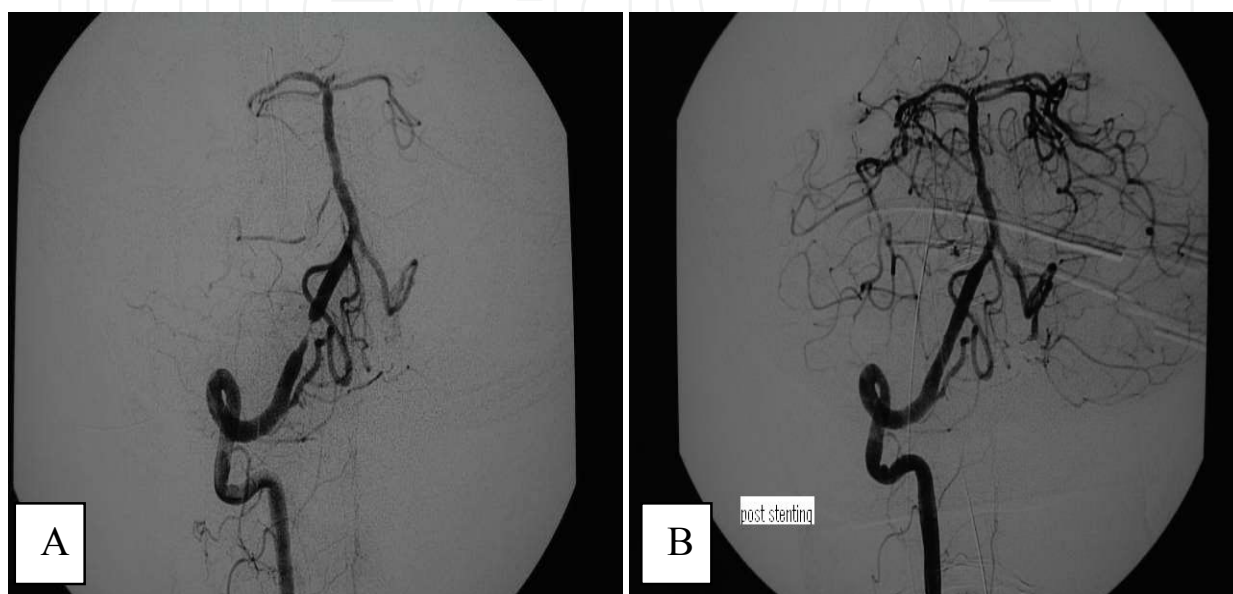


Fig. 2. DSA images showing disease in Right vertebral artery. A) Tight stenosis in Right vertebral artery, B) Post stenting restoration of flow. (Image Courtesy: Dr. Tanveer-ul-Haq, Associate Professor, Section Head, Vascular and Interventional Radiology, Radiology Department, Aga Khan University Hospital, Karachi, Pakistan)

When conducted for diagnostic purposes, risk associated with the procedure has gone down over the past years. The most recent estimate quotes the risk of stroke at 0.03% and of arterial dissections at 0.14%. The non-neurologic complications related to the arterial puncture were also not commonly seen (Fifi et al, 2009). In a dedicated unit for cerebral angiographies, the risk of neurologic complications can approach zero (Thiex et al, 2010). Interestingly, the risk of neurological adverse events was higher in patients with known intracranial atherosclerotic disease who underwent cerebral angiography in the WASID trial. 2% of these patients experienced neurological symptoms although all were transient and 6.1% had non-neurologic complications (Cloft et al, 2011).

Given the disadvantages of DSA and the increased morbidity and potential mortality associated with it, non-invasive modalities are increasingly being utilized for assessment of intracranial atherosclerotic disease.

## 4.2 Magnetic Resonance Angiography (MRA)

### 4.2.1 Phase contrast (PC) and Time of Flight (TOF) MRA

Phase contrast MRA utilizes the velocity differences and hence the phase shifts in moving spins to provide image contrast in flowing vessels. The phase of magnetization from the

moving spins is taken as non-zero and that from the stationary spins is zero. Time of Flight MRA depends on the flow and movement of protons in blood through the imaging plane. It derives contrast between flowing blood and stationary tissues by manipulating the magnitude of magnetization. From the moving spins the magnitude is large and from static spins it is small. Both techniques can be used using two or three-dimensional acquisition although 3-D images have a long acquisition time.

The main advantage of the modality lies in its non-invasive nature. There is no radiation exposure and no iodinated contrast exposure. It requires very little user interaction for acquisition and processing of images. When compared to the gold standard DSA, TOF-MRA has sensitivity in the range of 70% for intracranial stenosis and 81% for occlusion and a negative predictive value of 98% for stenosis and 99% for occlusion (Bash et al, 2005). Another study identified 87% negative predictive value for detecting a greater than 50% stenosis (Feldmann et al, 2007). These results may be slightly improved by use of Maximum Intensity Projections (MIP).

There are however, several limitations when using PC and TOF MRA for intracranial stenosis evaluation. Firstly since it depends on changes in blood flow, it is prone to motion artifacts and to changes in the direction of the flow. The spatial resolution is also inferior to DSA and CTA. Another major drawback is its inability to distinguish between high grade stenosis and occlusion. Stenotic lesions are sites where complex, slow or in-phase flow characteristics are seen (Furst et al, 1995). Because of this there are proton spin dephasing artifacts and flow signal intensity loss is seen at severely narrowed sites. In addition, TOF technique requires longer imaging time.

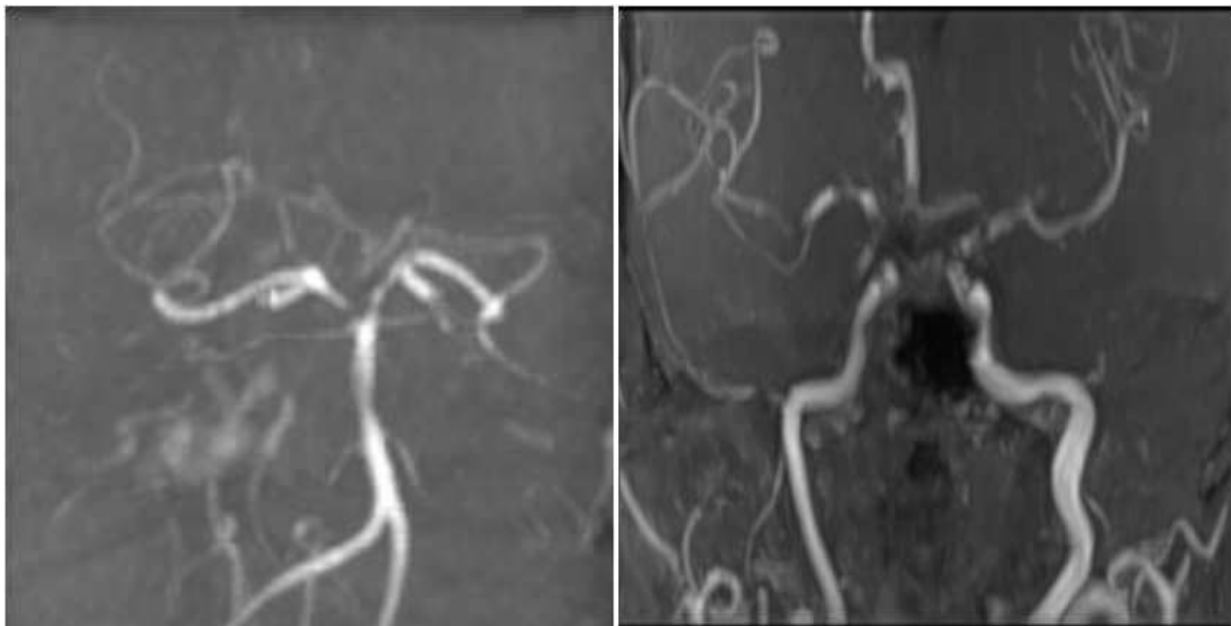


Fig. 3. TOF-MRA images of intracranial stenosis. A) Stenosis seen in bilateral PCAs, B) Severe atherosclerotic disease in supraclinoid ICA, bilateral MCA and ACA. (Image Courtesy, Stroke Fellowship Program, Aga Khan University Hospital, Karachi, Pakistan)

#### 4.2.2 Contrast Enhanced (CE) MRA

Some of the disadvantages of TOF and PC MRA can be overcome with the use of gadolinium dye. CE-MRA utilizes the time of flight technique along with use of contrast

agent to shorten the T1 of the blood so that in the first pass of the contrast agent, the arteries show up in striking contrast to the surrounding stationary tissues and veins. The CE MRA provides better anatomic delineation of vascular structures and can better assess areas of changing flow direction. This is because the technique depends on the intrinsic T1 signal of blood, rather than the flow characteristics and is minimally affected by dephasing seen with complex flow.

A certain degree of expertise is needed to time the image acquisition to minimize venous contamination. If the image is taken too early, arteries will not contrast enhance and if it is taken too late, the image will be contaminated by contrast uptake in the veins and surrounding tissues. For external carotids it is a widely used technique, but for assessment of intracranial vasculature it is still underutilized.

#### **4.2.3 Quantitative MRA (QMRA)**

Quantitative MRA (QMRA) is a newer technique that utilizes TOF and Phase contrast MRI to determine the vessel anatomy and measure blood flow. This allows for hemodynamic assessment of areas supplied by stenotic vessels. The technique has been shown to be particularly useful in prognosticating future risk of stroke in symptomatic vertebrobasilar disease. Those found to have a low distal flow on QMRA had a 71% stroke free survival at 2 years as opposed to a 100% stroke free survival for those with a normal flow (Amin-Hanjani et al, 2005).

QMRA has also found utility in assessment of flow before and after stent placement (Brisman, 2008). More importantly for in-stent restenosis it is now an evolving non-invasive technique. In these patients, CTA and MRA are not of use due to the artifacts produced by the stent and DSA continues to be the mainstay for assessment of stent thrombosis. Recently QMRA has shown promise as a screening tool for in-stent stenosis with 100% sensitivity and negative predictive value and 92% specificity (Prabhakaran et al, 2009). QMRA can also be used to determine regional blood flow and indicate the adequacy of collateral flow and overall cerebral hemodynamics in patients of intracranial atherosclerotic disease (Zhao et al, 2007).

#### **4.2.4 High Resolution MRI (HR-MRI)**

Another emerging technique is HR-MRI which allows for imaging of the atherosclerotic plaque. It creates sufficiently thin slices through the vessel wall to allow for determination of plaque size, composition and biological activity (Yuan et al, 2006). This modality can also help discriminate from other non-atherosclerotic etiologies of vessel narrowing.

Determination of plaque composition in terms of lipids, fibrous tissue and calcium and plaque activity in terms of inflammation can help determine whether a plaque is vulnerable or stable. HR MRI can also detect intraplaque hemorrhage which is another marker of plaque instability and can help predict risk of future vascular events (Turan et al, 2009 and Altaf et al, 2007). Furthermore, imaging the plaque directly can help determine presence of non-stenotic lesions which are generally missed with conventional MRA. Particularly in the evaluation of basilar artery, it was found that HR MRI detected atherosclerotic disease as a cause of pontine infarction in 42% of cases where TOF MRA and CE MRA had failed to show any basilar disease (Klein et al, 2010). Recently the technique has also found utility in guiding endovascular intervention of basilar artery (Jiang et al, 2011).

In future, HR MRI can potentially provide targets for intervention at an early stage of intracranial atherosclerotic disease, detect non stenotic atherosclerotic lesions, and predict future risk of vascular events based on plaque morphology and characteristics.



### 4.3 Computerized Tomography Angiography (CTA)

Computed tomography (CT) angiography is a relatively new non-invasive procedure that allows for accurate visualization of vascular structures and differentiates them from adjacent bone and soft tissues. Helical or Spiral CTA is acquired with the X-ray tube continuously rotating in a 360 degree turn while the table transports the patient slowly through the scanner. The slice thickness and the scan time for each helical series determine the extent of anatomic coverage. Axial images are stacked to form a volume of image data that can be processed in various formats like maximum intensity projection, multiplanar reformation and shaded surface display. This allows for 3 dimensional reconstruction of vessels similar to DSA.

An iodinated contrast is injected through a peripheral vein and both arterial and venous phases can be easily obtained. Unlike MRA, CTA is not dependent on flow characteristics of the blood. Instead it relies on relative penetrance of the contrast agent within the blood vessel. New scanners allow smaller slice thickness and hence greater resolution. Additionally, three-dimensional reformatting allows for excellent appreciation of anatomic relationships between bones, soft tissues, and the vascular system. Spiral or helical CTA is now used commonly for the evaluation of intracranial stenosis and provides excellent anatomic visualization.

The sensitivity of CTA for detection of intracranial occlusion is almost 100% compared to DSA (Nguyen-Huynh et al, 2008 and Bash et al, 2005). For detection of stenotic lesions greater than 50%, the sensitivity is 97.1% and specificity is 99.5%. With this high sensitivity and specificity it is an excellent tool for screening people with intracranial stenosis. Helical CTA has also been shown to be superior to DSA in detecting vessel patency in posterior circulation where low flow states can produce an impression of occlusion on DSA (Bash et al, 2005).

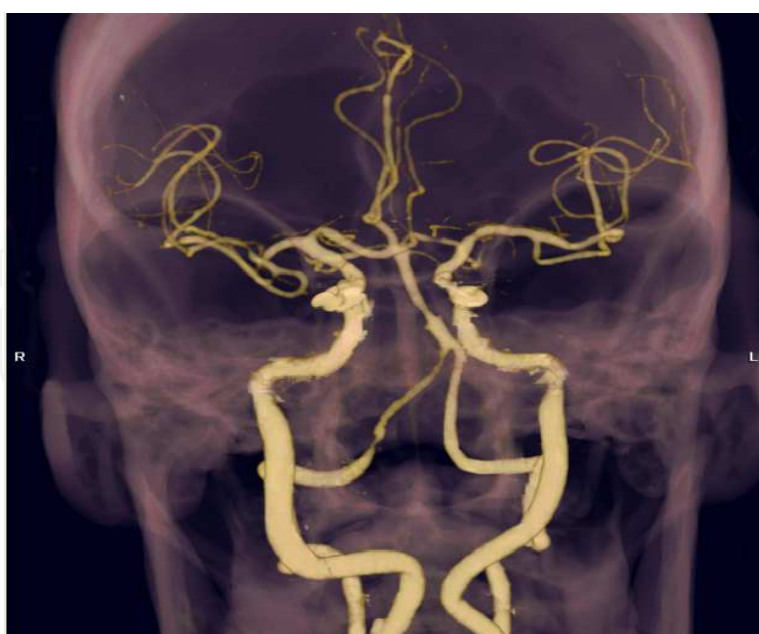


Fig. 4. CTA image demonstrating stenotic lesions in right vertebral, right M2 segment and left M1 segment of MCA. (Image Courtesy: Dr. Tanveer-ul-Haq, Associate Professor ,Section Head, Vascular and Interventional Radiology, Radiology Department, Aga Khan University Hospital , Karachi, Pakistan.)

The major advantage of CTA lies in its non-invasive nature compared to DSA and better image quality compared to MRA. It takes less time for acquisition of images; it is not affected by motion artifacts and is independent of hemodynamic effects seen with MRA. There is also a high inter-reader reliability in quantitation of stenotic lesions (Bash et al, 2005). Another major advantage over MRA lies in the ability of CTA to accurately depict areas of low flow distal to severely stenotic vessels (Skutta et al, 1999 and Bash et al, 2005). It was previously thought that petrous and cavernous ICA are regions elusive to CTA due to bony or calcium artifacts (Skutta et al, 1999 and Hirai et al 2002). However, newer studies do not report this problem likely because of better post processing and acquisition techniques (Bash et al, 2005).

Limitations of CTA include radiation exposure and risk of nephrotoxicity with the use of intravenous contrast agent. Another limitation to the technique is skill required for optimal contrast gradient-timing to avoid venous contamination and for post processing of the images to avoid contamination with surrounding structures. For accurate visualization of vessels to avoid over or underestimation of stenosis, there is a need for optimally adjusting window and level settings (Bash et al, 2005). CTA may be inferior to MRA in certain respects as it provides no information on flow characteristics across a stenotic lesion.

#### 4.4 Transcranial Doppler (TCD)

Transcranial Doppler (TCD) is a useful, non invasive, real time and portable mechanism of investigating 50 to 99% stenosis of the intracranial arteries. Ultrasound is a travelling wave of energy that has a frequency of more than 20,000 Hz which is above the audible range for humans. The Doppler effect, first described by Christian Andreas Doppler, is the change or shift in the frequency or wavelength of a wave due to relative movement between the sound scatterer and the receiver. In TCD, the Doppler effect can be used to determine the speed and direction of flow in blood vessels. Many red blood cells move at varying speeds through an insonated vessel and the TCD sample volume is relatively large. The signal received from any sample volume within a vessel is a mixture of the different Doppler frequency shifts forming a spectrum that is displayed visually.

Low frequency ultrasound can penetrate the skull; the temporal bone is the thinnest portion of the skull and allows successful insonation. An inadequate temporal window is a major cause of insufficient evaluation of cerebral vessels during TCD. The prevalence of this finding is 14.5% and is increased in non white females greater than 60 years of age. (Ratanakorn, 1998). The temporal window allows the ICA, MCA, ACA to be sampled, the occipital allows the posterior circulation to be reviewed, and the ophthalmic allows the collateral information to be gathered.

Spectral waveforms are identified by their direction, depth of insonation, velocity characteristics, and spectral measurements are then performed to report the following parameters for the cerebral circulation: Mean Flow Velocity (MFV) and the Pulsatility Index (PI).

$$MFV = (PSV + 2 EDV) / 3 \quad (1)$$

$$PI = (PSV - EDV) / MFV \quad (2)$$

where PSV= Peak Systolic Velocity and EDV= End Diastolic Velocity

MFV correlates well with vessel patency and degree of arterial stenosis. The PI is an indirect measure of peripheral resistance. Post stenotic vessels with blunted waveforms have low

resistance and chronic hypertensives have high PI. In addition TCD can provide information on the presence or absence of microembolic signals and the progression and regression of stenosis.

The advantages of TCD are that the vessels are insonated non-invasively, at the bedside and repeatedly without any harm to the patients. The limitations of TCD include a lack of windows, operator dependency, and the fact that lesser degrees of stenosis are not picked up and that direct evaluation is limited to the basal intracranial vessels.

TCD is a useful adjunct to the diagnosis of ICAD in the following ways

#### 1. Non invasive diagnosis of 50 – 70% stenosis and response to therapy

Velocity thresholds that predict a significant MCA stenosis have been reported. As a rule in a vessel with straight walls a 50% diameter reduction doubles the velocity and a 70 % stenosis can quadruple the velocity at the exit of the stenosis compared with a prestenotic segment or to the contralateral side.

The criteria that are used include MFV, Peak systolic velocity (PSV) and stenotic to prestenotic ratios. The velocity criteria for determining the degree of stenosis in the different vessels are reported from the SONIA study that in addition, reported the Positive and Negative predictive values (PPV and NPV). When using non invasive imaging it is important to correlate the status of the extracranial carotid artery. Collateral flow and decreased volume flow from the proximal carotid stenosis without adequate collateral flow results in false positive and false negative interpretations respectively. To further help avoid false positives a prestenotic to post stenotic MCA velocity ration of 1 :  $\geq 2$  should be used in addition to the MFV threshold.

The relative portability of TCD has led to wide scale applications in population screenings to detect asymptomatic disease and to follow the regression of stenosis and response to therapy in large scale interventional studies. It has therefore been used as a biologic surrogate marker much like carotid Intima media Thickness (IMT). However, it is not clear at this point whether the regressive changes in TCD can predict clinically important amelioration of outcomes.

#### 2. Characterization of Microembolic Signals (MES)

When following standardized assessment, the detection of microembolic signals in stenotic arteries in real time can predict the appearance of stroke (Garami and Alexandrov, 2008). Microembolic signals are common in patients with large artery disease and are an independent marker of future stroke risk of intracranial stenosis. In the CLAIR study (Wong et al, 2010) the administration of two antiplatelet agents reduced the appearance of MES in patients with Intracranial stenosis who were given aspirin and clopidogrel within 7 days of their stroke. Whether this reduction in microembolic activity results in reduction of the occurrence of stroke remains to be tested in large scale clinical trials.

#### 3. Adequacy of Collaterals and Vasomotor Reactivity

Collaterals have a significant effect on stroke outcomes, and with very severe stenoses they are shown to have a protective effect as opposed to lesser degrees of stenoses in which case the presence of collaterals signifies a greater instability (Liebeskind et al, 2010). TCD can help in evaluation of collaterals at the circle of Willis. Leptomeningeal and other secondary collaterals cannot be evaluated with this technique. Contrast addition to the imaging can help improve its sensitivity. Tests of vasomotor reactivity are also used to assess the adequacy of collaterals. A vasodilatory challenge can be given such as acetazolamide, or

CO<sub>2</sub> inhalation or apnea. Impaired vasomotor reactivity with CO<sub>2</sub> has been tested with TCD and shown to correlate with stroke risk in patients with carotid stenosis (Visser et al, 2000).

#### 4.5 Hemodynamic monitoring

Direct visualization of the vessels using the above techniques gives a reliable estimate of the anatomic degree of stenosis. Since intracranial atherosclerotic disease is a slowly progressive condition, it leads to chronic hypoperfusion and development of collaterals. The development of collaterals does not guarantee their persistence and they are also prone to hemodynamic fluctuations and occlusion secondary to artery to artery embolization in cases where they originate from cortical vessels. These collaterals can also be visualized using the vessel imaging techniques already described. Whether these collaterals are adequate to maintain perfusion in the territory of stenotic vessel needs evaluation with other modalities of which TCD has already been discussed.

Blood flow through the capillaries is referred to as perfusion and this is responsible for delivering oxygen to the brain tissue. Cerebral blood flow (CBF) and blood volume (CBV) are indicators of brain perfusion. Regional cerebral blood flow is proportional to the regional cerebral metabolism. Initial compensatory mechanism to deal with a decrease in perfusion is vasodilatation. Once maximum vasodilation has occurred, oxygen extraction fraction increases to maintain the metabolic needs of the cerebral tissue. Regional cerebrovascular reserve (rCVR) is another parameter that can be measured to gauge the vasodilatory capacity of the arterioles.

Several techniques are now available to measure perfusion through the brain. These include positron emission tomography (PET), single-photon emission CT (SPECT), xenon-enhanced CT, perfusion CT and MRI, and TCD. Addition of acetazolamide challenge to various imaging modalities increases their sensitivity for picking up decreased rCVR.

PET imaging measures cerebral oxygen extraction fraction (OEF) and has been the gold standard so far for identifying hemodynamic failure (Derdeyn et al, 2002). It allows for measurement of CBF, CBV and Mean Transit Time (MTT). It is currently being used to select patients with poor hemodynamic reserve, secondary to ICAD, eligible for external to internal carotid bypass. The benefit of this procedure can then also be gauged by imaging, translating as improved oxygen perfusion in previously occluded areas. Small retrospective studies have shown the outcome of external to internal bypass to be favorable (Nagata et al, 1991 and Mendelowitsch et al, 2004). PET is restricted in its utility because of its high cost and limited availability.

SPECT can be similarly utilized to measure rCVR and when used with acetazolamide challenge it provides additional information regarding hemodynamic status of the brain (Ozgur et al, 2001). This again has been utilized to judge the dependency on external carotid-internal carotid (EC-IC) and leptomeningeal collaterals. Use of acetazolamide challenge allows for assessment of vasomotor reactivity (VMR) as well which when impaired predicts future stroke. Although SPECT is more widely available compared to PET, its disadvantage lies in longer imaging time and inferior spatial resolution (Eskey and Sanelli, 2005).

Two major trials are currently ongoing to recruit patients with poor hemodynamic reserve secondary to atherosclerotic disease and to evaluate the effectiveness of the bypass procedure. These include the Carotid Occlusion Surgery Study in US (COSS) (Grubb et al, 2003) which is using PET and the Japanese EC-IC bypass Trial (JET) (Mizumura et al, 2004) which is utilizing SPECT for hemodynamic monitoring. They have so far validated the imaging modalities to recruit candidates for the procedure.



Perfusion studies using CT and MRI can also reliably estimate CVR in patients with intracranial stenosis. Perfusion CT provides quantitative values for CBF, CBV and MTT and has recently been shown to have a significant correlation with SPECT parameters. MTT was the most predictive of a decreased CVR in this study even without use of acetazolamide challenge (Kim et al, 2009).

Xenon-enhanced computed tomography (XeCT) has been in use for the past two decades to measure cerebral blood flow and is frequently utilized by revascularization experts to calculate the cerebrovascular reserve capacity (Wintermark et al, 2001). Its major advantage lies in its superior spatial resolution, accuracy, and reproducibility. Xenon gas is inhaled and its concentration is measured in the brain by CT scanner. There is a potential for adverse reaction to the gas besides radiation exposure and motion artifacts can also affect image quality (Wintermark et al, 2005).

To conclude several techniques are available for assessment of cerebral hemodynamics. Each carries its own advantages and disadvantages. PET due to its expense and limited availability is restricted in its utilization, but SPECT and Perfusion CT are reasonable alternatives.

## 5. Conclusion

Intracranial atherosclerosis is the progressive atherosclerotic stenosis of the arteries at the base of the brain. This condition is responsible for 10 – 50% of ischemic strokes worldwide. It is more common in Asians, Hispanics, Blacks and South East Asians and thus in absolute numbers is probably the most common cause of stroke in the world. Radiologically, it presents with border-zone ischemia, either in the internal border-zone area or the distal cortical area, with discrete cortical infarction or a lacunar perforator infarction with involvement of the parent vessel. The intracranial stenosis and its associated collaterals can be best quantified by catheter angiography, however this is invasive and not entirely without risk. Non invasively, MRA, CTA and TCD all offer valuable and complementary information. MRA can assess flow and stenosis, however it may overestimate preocclusive stenosis. CTA may be useful in these settings where actual anatomic accuracy is needed to differentiate preocclusive stenosis from complete occlusion since it is not flow dependent. TCD provides real time hemodynamic information to delineate the mechanism of stroke in the individual patient – whether it is a flow related hemodynamic stroke, whether or not regression has occurred or that the patient has microemboli from platelet aggregation. Additionally TCD has good negative predictive value in reporting 50 – 90% stenosis. It is postulated that stenosis of less than 50% may also be responsible for stroke through embolizations from unstable plaque. However, very little is known about this entity except that High resolution MRI can visualize these plaques in vivo. For those with high grade progressive stenosis, the prognosis clearly depends on the extent of collateralization. This can be investigated with PET, SPECT and perfusion CT to best select patients for EC\_IC Bypass procedures which are currently investigational.

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## 7. References

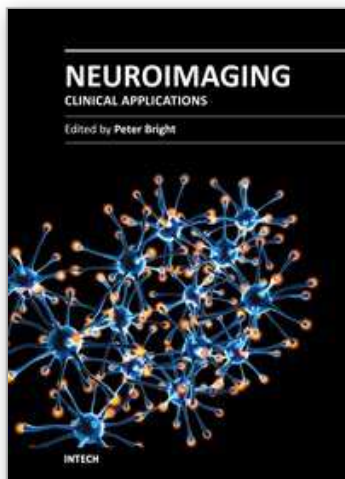
- Altaf, N., Beech, A., Goode, S.D., Gladman, J.R., Moody, A.R., Auer, D.P., & MacSweeney, S.T. (2007) Carotid intraplaque hemorrhage detected by magnetic resonance imaging predicts embolization during carotid endarterectomy. *J Vasc Surg*, 46, 31-36. ISSN 0741-5214
- Amarenco, P., Levy, C., Cohen, A., Touboul, P.J., Roullet, E., & Bousser, M.G. (1994) Causes and mechanisms of territorial and nonterritorial cerebellar infarcts in 115 consecutive patients. *Stroke*, 25, 105-112. ISSN 0039-2499
- Amin-Hanjani, S., Du, X., Zhao, M., Walsh, K., Malisch, T.W., & Charbel, F.T. (2005) Use of quantitative magnetic resonance angiography to stratify stroke risk in symptomatic vertebrobasilar disease. *Stroke*, 36, 1140-1145. ISSN 0039-2499
- Bash, S., Villablanca, J.P., Jahan, R., Duckwiler, G., Tillis, M., Kidwell, C., Saver, J., & Sayre, J. (2005) Intracranial vascular stenosis and occlusive disease: evaluation with CT angiography, MR angiography, and digital subtraction angiography. *AJNR Am J Neuroradiol*, 26, 1012-1021. ISSN 0195-6108
- Belden, J.R., Caplan, L.R., Pessin, M.S., & Kwan, E. (1999) Mechanisms and clinical features of posterior border-zone infarcts. *Neurology*, 53, 1312-1318. ISSN 0028-3878
- Bogousslavsky, J., & Regli, F. (1992) Centrum ovale infarcts: subcortical infarction in the superficial territory of the middle cerebral artery. *Neurology*, 42, 1992-1998. ISSN 0028-3878
- Brisman, J.L. (2008) Wingspan stenting of symptomatic extracranial vertebral artery stenosis and perioperative evaluation using quantitative magnetic resonance angiography: report of two cases. *Neurosurg Focus*, 24, E14. ISSN 1092-0684
- Cloft, H.J., Lynn, M.J., Feldmann, E., & Chimowitz, M. Risk of Cerebral Angiography in Patients with Symptomatic Intracranial Atherosclerotic Stenosis. *Cerebrovasc Dis*, 31, 588-591. ISSN 1015-9770
- Derdeyn, C.P., Videen, T.O., Yundt, K.D., Fritsch, S.M., Carpenter, D.A., Grubb, R.L., & Powers, W.J. (2002) Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. *Brain*, 125, 595-607. ISSN 0006-8950
- Eskey, C.J., & Sanelli, P.C. (2005) Perfusion imaging of cerebrovascular reserve. *Neuroimaging Clin N Am*, 15, 367-381, xi. ISSN 1052-5149
- Felberg, R.A., Christou, I., Demchuk, A.M., Malkoff, M., & Alexandrov, A.V. (2002) Screening for intracranial stenosis with transcranial Doppler: the accuracy of mean flow velocity thresholds. *J Neuroimaging*, 12, 9-14. ISSN 1051-2284
- Feldmann, E., Wilterdink, J.L., Kosinski, A., Lynn, M., Chimowitz, M.I., Sarafin, J., Smith, H.H., Nichols, F., Rogg, J., Cloft, H.J., Wechsler, L., Saver, J., Levine, S.R., Tegeler, C., Adams, R., & Sloan, M. (2007) The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. *Neurology*, 68, 2099-2106. ISSN 0028-3878

- Fifi, J.T., Meyers, P.M., Lavine, S.D., Cox, V., Silverberg, L., Mangla, S., & Pile-Spellman, J. (2009) Complications of modern diagnostic cerebral angiography in an academic medical center. *J Vasc Interv Radiol*, 20, 442-447. ISSN 1051-0443
- Furst, G., Hofer, M., Sitzler, M., Kahn, T., Muller, E., & Modder, U. (1995) Factors influencing flow-induced signal loss in MR angiography: an in vitro study. *J Comput Assist Tomogr*, 19, 692-699. ISSN 0363-8715
- Garami, Z., & Alexandrov, A.V. (2009) Neurosonology. *Neurol Clin*, 27, 89-108, viii. ISSN 0733-8619
- Grubb, R.L.Jr., Powers, W.J., Derdeyn, C.P., Adams, H.P.Jr., & Clarke, W.R. (2003) The Carotid Occlusion Surgery Study. *Neurosurg Focus*, 14, e9. ISSN 1092-0684
- Hirai, T., Korogi, Y., Ono, K., Nagano, M., Maruoka, K., Uemura, S., & Takahashi, M. (2002) Prospective evaluation of suspected stenooclusive disease of the intracranial artery: combined MR angiography and CT angiography compared with digital subtraction angiography. *AJNR Am J Neuroradiol*, 23, 93-101. ISSN 0195-6108
- Huang, Y.N., Gao, S., Li, S.W., Huang, Y., Li, J.F., Wong, K.S., & Kay, R. (1997) Vascular lesions in Chinese patients with transient ischemic attacks. *Neurology*, 48, 524-525. ISSN 0028-3878
- Kang, D.W., Latour, L.L., Chalela, J.A., Dambrosia, J., & Warach, S. (2003) Early ischemic lesion recurrence within a week after acute ischemic stroke. *Ann Neurol*, 54, 66-74. ISSN 0364-5134
- Kim, E., Sohn, C.H., Na, D.G., Kim, J.E., Chang, K.H., Kim, J.H., & Jeon, S.J. (2009) Perfusion computed tomography evaluation of cerebral hemodynamic impairment in patients with unilateral chronic steno-occlusive disease: a comparison with the acetazolamide challenge 99mTc-hexamethylpropyleneamine oxime single-photon emission computed tomography. *J Comput Assist Tomogr*, 33, 546-551. ISSN 0363-8715
- Kim, J.T., Yoo, S.H., Kwon, J.H., Kwon, S.U., & Kim, J.S. (2006) Subtyping of ischemic stroke based on vascular imaging: analysis of 1,167 acute, consecutive patients. *J Clin Neurol*, 2, 225-230. ISSN 1738-6586
- Klein, I.F., Lavalley, P.C., Mazighi, M., Schouman-Claeys, E., Labreuche, J., & Amarenco, P. Basilar artery atherosclerotic plaques in paramedian and lacunar pontine infarctions: a high-resolution MRI study. *Stroke*, 41, 1405-1409. ISSN 0039-2499
- Lee, D.K., Kim, J.S., Kwon, S.U., Yoo, S.H., & Kang, D.W. (2005) Lesion patterns and stroke mechanism in atherosclerotic middle cerebral artery disease: early diffusion-weighted imaging study. *Stroke*, 36, 2583-2588. ISSN 0039-2499
- Lee, S.J., Cho, S.J., Moon, H.S., Shon, Y.M., Lee, K.H., Kim, D.I., Lee, B.B., Byun, H.S., Han, S.H., & Chung, C.S. (2003) Combined extracranial and intracranial atherosclerosis in Korean patients. *Arch Neurol*, 60, 1561-1564. ISSN 0003-9942
- Liebeskind, D.S., Cotsonis, G.A., Saver, J.L., Lynn, M.J., Turan, T.N., Cloft, H.J., & Chimowitz, M.I. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. *Ann Neurol*. ISSN 0364-5134
- Masuda, J., Yutani, C., Ogata, J., Kuriyama, Y., & Yamaguchi, T. (1994) Atheromatous embolism in the brain: a clinicopathologic analysis of 15 autopsy cases. *Neurology*, 44, 1231-1237. ISSN 0028-3878
- Mazighi, M., Tanasescu, R., Ducrocq, X., Vicaut, E., Bracard, S., Houdart, E., & Woimant, F. (2006) Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. *Neurology*, 66, 1187-1191. ISSN 0028-3878
- Mendelowitsch, A., Taussky, P., Rem, J.A., & Gratzl, O. (2004) Clinical outcome of standard extracranial-intracranial bypass surgery in patients with symptomatic

- atherosclerotic occlusion of the internal carotid artery. *Acta Neurochir (Wien)*, 146, 95-101. ISSN 0001-6268
- Mizumura, S., Nakagawara, J., Takahashi, M., Kumita, S., Cho, K., Nakajo, H., Toba, M., & Kumazaki, T. (2004) Three-dimensional display in staging hemodynamic brain ischemia for JET study: objective evaluation using SEE analysis and 3D-SSP display. *Ann Nucl Med*, 18, 13-21. ISSN 0914-7187
- Nagata, S., Fujii, K., Matsushima, T., Fukui, M., Sadoshima, S., Kuwabara, Y., & Abe, H. (1991) Evaluation of EC-IC bypass for patients with atherosclerotic occlusive cerebrovascular disease: clinical and positron emission tomographic studies. *Neurol Res*, 13, 209-216. ISSN 0161-6412
- Nahab, F., Cotsonis, G., Lynn, M., Feldmann, E., Chaturvedi, S., Hemphill, J.C., Zweifler, R., Johnston, K., Bonovich, D., Kasner, S., & Chimowitz, M. (2008) Prevalence and prognosis of coexistent asymptomatic intracranial stenosis. *Stroke*, 39, 1039-1041. ISSN 0039-2499
- Nguyen-Huynh, M.N., Wintermark, M., English, J., Lam, J., Vittinghoff, E., Smith, W.S., & Johnston, S.C. (2008) How accurate is CT angiography in evaluating intracranial atherosclerotic disease? *Stroke*, 39, 1184-1188. ISSN 0039-2499
- Ozgur, H.T., Kent Walsh, T., Masaryk, A., Seeger, J.F., Williams, W., Krupinski, E., Melgar, M., & Labadie, E. (2001) Correlation of cerebrovascular reserve as measured by acetazolamide-challenged SPECT with angiographic flow patterns and intra- or extracranial arterial stenosis. *AJNR Am J Neuroradiol*, 22, 928-936. ISSN 0195-6108
- Park, K.Y., Chung, C.S., Lee, K.H., Kim, G.M., Kim, Y.B., & Oh, K. (2006) Prevalence and risk factors of intracranial atherosclerosis in an asymptomatic Korean population. *J Clin Neurol*, 2, 29-33. ISSN 1738-6586
- Pollanen, M.S., & Deck, J.H. (1990) The mechanism of embolic watershed infarction: experimental studies. *Can J Neurol Sci*, 17, 395-398. ISSN 0317-1671
- Prabhakaran, S., Warrior, L., Wells, K.R., Jhaveri, M.D., Chen, M., & Lopes, D.K. (2009) The utility of quantitative magnetic resonance angiography in the assessment of intracranial in-stent stenosis. *Stroke*, 40, 991-993. ISSN 0039-2499
- Ratanakorn, D., Kremkau, F.W., Myers, L.G., Meads, D.B., & Tegeler, C.H. (1998) Mirror-image artifact can affect transcranial Doppler interpretation. *J Neuroimaging*, 8, 175-177. ISSN 1051-2284
- Roh, J.K., Kang, D.W., Lee, S.H., Yoon, B.W., & Chang, K.H. (2000) Significance of acute multiple brain infarction on diffusion-weighted imaging. *Stroke*, 31, 688-694. ISSN 0039-2499
- Rorick, M.B., Nichols, F.T., & Adams, R.J. (1994) Transcranial Doppler correlation with angiography in detection of intracranial stenosis. *Stroke*, 25, 1931-1934. ISSN 0039-2499
- Rovira, A., Grive, E., & Alvarez-Sabin, J. (2005) Distribution territories and causative mechanisms of ischemic stroke. *Eur Radiol*, 15, 416-426. ISSN 0938-7994
- Sacco, R.L., Kargman, D.E., Gu, Q., & Zamanillo, M.C. (1995) Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. *Stroke*, 26, 14-20. ISSN 0039-2499
- Skutta, B., Furst, G., Eilers, J., Ferbert, A., & Kuhn, F.P. (1999) Intracranial stenooclusive disease: double-detector helical CT angiography versus digital subtraction angiography. *AJNR Am J Neuroradiol*, 20, 791-799. ISSN 0195-6108
- Thiex, R., Norbash, A.M., & Frerichs, K.U. The safety of dedicated-team catheter-based diagnostic cerebral angiography in the era of advanced noninvasive imaging. *AJNR Am J Neuroradiol*, 31, 230-234. ISSN 0195-6108

- Torvik, A., & Skullerud, K. (1982) Watershed infarcts in the brain caused by microemboli. *Clin Neuropathol*, 1, 99-105. ISSN 0722-5091
- Turan, T.N., Bonilha, L., Morgan, P.S., Adams, R.J., & Chimowitz, M.I. Intraplaque hemorrhage in symptomatic intracranial atherosclerotic disease. *J Neuroimaging*, 21, e159-161. ISSN 1051-2284
- Turtzo, L.C., Gottesman, R.F., & Llinas, R.H. (2009) Diffusion-weighted imaging showing 'pearls' predicts large-vessel disease as stroke etiology. *Cerebrovasc Dis*, 28, 49-54. ISSN 1015-9770
- Wintermark, M., Thiran, J.P., Maeder, P., Schnyder, P., & Meuli, R. (2001) Simultaneous measurement of regional cerebral blood flow by perfusion CT and stable xenon CT: a validation study. *AJNR Am J Neuroradiol*, 22, 905-914. ISSN 0195-6108
- Wintermark, M., Sesay, M., Barbier, E., Borbely, K., Dillon, W.P., Eastwood, J.D., Glenn, T.C., Grandin, C.B., Pedraza, S., Soustiel, J.F., Nariai, T., Zaharchuk, G., Caille, J.M., Dousset, V., & Yonas, H. (2005) Comparative overview of brain perfusion imaging techniques. *J Neuroradiol*, 32, 294-314. ISSN 0150-9861
- Wityk, R.J., Lehman, D., Klag, M., Coresh, J., Ahn, H., & Litt, B. (1996) Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke*, 27, 1974-1980. ISSN 0039-2499
- Wong, K.S., Li, H., Chan, Y.L., Ahuja, A., Lam, W.W., Wong, A., & Kay, R. (2000) Use of transcranial Doppler ultrasound to predict outcome in patients with intracranial large-artery occlusive disease. *Stroke*, 31, 2641-2647. ISSN 0039-2499
- Wong, K.S., Gao, S., Chan, Y.L., Hansberg, T., Lam, W.W., Droste, D.W., Kay, R., & Ringelstein, E.B. (2002) Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis: a diffusion-weighted imaging and microemboli monitoring study. *Ann Neurol*, 52, 74-81. ISSN 0364-5134
- Wong, K.S., Ng, P.W., Tang, A., Liu, R., Yeung, V., & Tomlinson, B. (2007) Prevalence of asymptomatic intracranial atherosclerosis in high-risk patients. *Neurology*, 68, 2035-2038. ISSN 0028-3878
- Wong, K.S., Chen, C., Fu, J., Chang, H.M., Suwanwela, N.C., Huang, Y.N., Han, Z., Tan, K.S., Ratanakorn, D., Chollate, P., Zhao, Y., Koh, A., Hao, Q., & Markus, H.S. (2010) Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol*, 9, 489-497. ISSN 1474-4422
- Yamauchi, H., Nishii, R., Higashi, T., Kagawa, S., & Fukuyama, H. (2009) Hemodynamic compromise as a cause of internal border-zone infarction and cortical neuronal damage in atherosclerotic middle cerebral artery disease. *Stroke*, 40, 3730-3735. ISSN 0039-2499
- Yong, S.W., Bang, O.Y., Lee, P.H., & Li, W.Y. (2006) Internal and cortical border-zone infarction: clinical and diffusion-weighted imaging features. *Stroke*, 37, 841-846. ISSN 0039-2499
- Yuan, C., Kerwin, W.S., Yarnykh, V.L., Cai, J., Saam, T., Chu, B., Takaya, N., Ferguson, M.S., Underhill, H., Xu, D., Liu, F., & Hatsukami, T.S. (2006) MRI of atherosclerosis in clinical trials. *NMR Biomed*, 19, 636-654. ISSN 0952-3480
- Zhao, M., Amin-Hanjani, S., Ruland, S., Curcio, A.P., Ostergren, L., & Charbel, F.T. (2007) Regional cerebral blood flow using quantitative MR angiography. *AJNR Am J Neuroradiol*, 28, 1470-1473. ISSN 0195-6108





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